Application Serial No. 07/955,012 filed September 30, 1992, now abandoned, and Application Serial No. 07/879,038 filed April 30, 1992, now abandoned, each of which is incorporated by reference herein in its entirety.--

On page 88, lines 4-5, delete "1201 Parklawn Drive, Rockville, Maryland 20852" and insert --10801 University Boulevard, Manassas, Virginia 20110-2209-- therefor.

IN THE CLAIMS

Please amend the claims as follows:

Please cancel claims 91-97, 99, 100, 102, 107, 108 and 113-123 without prejudice.

Please amend the following claims:

90 (once amended). A method for the manipulation of cell differentiation comprising contacting a cell with an amount of a molecule which promotes [or antagonizes] Notch function, effective to manipulate the differentiation of the contacted cell.

~~103~~ 4 (once amended). The method according to claim [92] ~~90~~ 1 wherein the molecule is a Delta protein.

~~105~~ 6 (once amended). The method according to claim [92] ~~90~~ 1 wherein the molecule is a Serrate protein.

REMARKS

The specification has been amended on page 1 to update the status of the priority applications, and on page 88 to update the address of the International Depository Authority which has recently moved to a new location. No new matter has been added by the amendments to the specification.

Claims 90, 98, 101, 103-106 and 109-112 are presently pending in the above-captioned application and claims 90, 98, 103, 106 and 106 are presently under consideration. Claims 101, 104, 105, 111 and 112 have been withdrawn from consideration as they claim subject matter directed to non-elected species. Claims 91, 93-97, 99, 100, 102, 107, 108 and 113-123 have been canceled without prejudice in view of the fact that they have been withdrawn from consideration as being drawn to a non-elected invention. Applicant reserves

the right to pursue the canceled claims directed to non-elected subject matter in one or more related applications. Claim 92 has been canceled in view of the amendment to claim 90, which renders claim 92 redundant.

With regard to the Examiner's statement on page 2 of the Office Action dated June 23, 1998 that the specification contemplates only antagonistic antibodies, Applicant points out that although the specification does not specifically disclose antibodies as agonists of Notch and does disclose that antibodies can be antagonists of Notch, the recitation of certain agonists and antagonists is merely exemplary. Applicant emphasizes that there is nothing in the specification that excludes activating antibodies as agonists of Notch function.

Claims 90, 103 and 105 have been amended to more particularly point out and distinctly claim the subject matter of the present invention. Specifically, claim 90 has been amended to remove reference to antagonizing Notch, and claims 103 and 105 have been amended to recite dependency from claim 90, rather than from canceled claim 92. Support for these amendments is found throughout the specification as filed. No new matter has been added by the amendments to the claims.

CLAIM OBJECTIONS

The Examiner has objected to claim 90 since claim 90 recites both promoting and antagonizing Notch function. In response, Applicant has amended claim 90 such that only promoting Notch function is recited. In view of the amendment to claim 90, Applicant submits that this objection has been obviated.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 90, 92, 98, 103, 106, 109 and 110 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that claims 90 and 109 are vague and indefinite in the recitation of "the manipulation of cell differentiation." The Examiner also alleges that claim 90 is further vague and indefinite in the recitation of "promotes Notch function", and claim 106 is vague and indefinite in the recitation of the term "Notch-group".

Applicant respectfully disagrees with the Examiner's allegations. The "distinctly claim" requirement of 35 U.S.C. § 112, second paragraph, means that the claims

must have a clear and definite meaning when construed in light of the complete patent document. Standard Oil Co. v. American Cyanamide Co., 774 F.2d 448, 227 U.S.P.Q. 293 (Fed. Cir. 1985). The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Orthokinetics, Inc. v. Safety Travel Chairs, Inc. 806 F.2d 1565, 1 U.S.P.Q.2d 1081 (Fed. Cir. 1986). A claim need not describe the invention, such description being provided by the specification's disclosure section. Id.

Applicant respectfully submits that the term "manipulating cell differentiation" is well known in the art and that one skilled in the art can clearly understand what is covered by this term. Applicant also points out that it is well settled law that when a term is not defined in the specification, the term is to be given its ordinary meaning, which ordinary meaning can be found in a dictionary.

> Absent . . . a definition [in the patent] or evidence that the claim limitation as a whole has a special meaning to one of skill in the art, we see no error in the district court's use of dictionary definitions to ascertain the ordinary meaning of the relevant claim limitation. Quantum Corp. v. Rodime, Plc. 65 F.3d 1577, 1581, 36 U.S.P.Q.2d 1162, 1166 (Fed. Cir. 1995).

Accordingly, Applicant submits herewith, as Exhibit A, page 825 of Webster's Third New International Dictionary of the English Language, G. & C. Merriam Co., pub., 1981 ("Webster's"), which recites the ordinary meaning of "manipulate".

According to Webster's, manipulate is defined as "[t]he act or practice of manipulating" and manipulating is defined as:

> 1. To operate or control by skilled use of the hands; handle. 2. To influence or manage shrewdly or deviously. . . 4. *Medic.* To handle and move in an examination or for therapeutic purposes.

Based on this art accepted meaning, Applicant submits that it is clear that to manipulate is to influence, and thus, to manipulate the differentiation state of a cell is to influence the differentiation state, *i.e.*, to alter or to maintain the differentiation state of a cell. Accordingly, Applicant submits that the term manipulation of cell differentiation would be understood by those of skill in the art to mean to alter or to maintain the differentiation state of a cell due to the intervention of the claimed methods. Thus, Applicant respectfully requests withdrawal of this Section 112 rejection.

Further, Applicant respectfully submits that the terms "promotes Notch function" and "Notch function" also would be clearly understood by those of skill in the art.

As described in the background section of the present application at pages 1-3, and as known to those of skill in the art, Notch is a transmembrane protein which is involved in a signaling pathway transducing extracellular signaling events (*e.g.*, binding of Delta to the extracellular domain) to the nucleus, which results in the alteration of gene transcription (*e.g.*, activation of basic helix-loop-helix (bHLH) genes in the Enhancer of Split complex). Further, the Examiner's attention is invited to the specification at page 16, lines 24-29 which states that:

> Notch functions as a receptor whose extracellular domain mediates ligand-binding, resulting in the transmission of developmental signals by the cytoplasmic domain. The phenotypes observed also suggested that the cdc10/ankyrin repeat region within the intracellular domain plays an essential role in Notch mediated signal transduction events (intracellular function).

Accordingly, a Notch function is understood as a function of the Notch protein or an activity of the Notch protein within this signal transduction pathway. Such functions include, but are not limited to, directly binding to Delta, Serrate, Deltex or Suppressor of Hairless, see, *e.g.*, Sections 6-8 of the present specification. Another function includes, but is not limited to, the ability to transduce an extracellular signaling event such that the transcription of certain bHLH genes within the Enhancer of Split complex is activated.

Moreover, each of these functions can be measured using methods well known in the art such that the promotion of such a function can readily be measured. Additionally, measuring the binding of Notch to Delta using cell aggregation assays, and immunoassays, are taught in the present specification. Accordingly, Applicant respectfully submits that the terms "Notch function" and "promoting Notch function" would be clearly understood by those of skill in the art, and thus, the withdrawal of this Section 112 rejection is respectfully requested.

Finally, Applicant disagrees with the Examiner's assertion that the term "Notch group of genes" is unclear. The Examiner states that the specification teaches that Notch group genes are identified by molecular and genetic interactions, including binding, however, there is no definition of what is included as an interaction and what is included as binding. Applicant submits that it is clear to those of skill in the art what exactly the meaning of the term "Notch group" is in view of the teaching of the specification at page 12, line 27 to page 13, line 2, wherein it states:

> Toporythmic genes, as used herein, shall mean the genes Notch, Delta, and Serrate, as well as other members of the Delta/Serrate family, which may be identified by virtue of sequence homology or genetic interaction, and, more generally, members of the "Notch cascade" or the "Notch group" of genes, which are identified by molecular interactions (*e.g.*, binding *in vitro*) or genetic interactions (as detected phenotypically, *e.g.*, in *Drosophila*).

With regard to the Examiner's allegation that there is no definition of interaction or binding, Applicant respectfully submits that these terms are well understood by those of skill in the art. As would be understood by one skilled in the art, an interaction, either molecular or genetic, is an interaction between members of the Notch group in which one member acts on the other member. See Webster's, page 707 (submitted as Exhibit B herewith) in which the ordinary meaning of interact is "[t]o act on each other." One manner of interaction is physical binding, *i.e.*, Delta binding with Notch. Another manner of interaction is an indirect interaction such as when Delta binds Notch, Suppressor of Hairless ("SuH") translocates to the nucleus. Although, Delta does not physically interact with SuH, Delta, by binding to Notch, acts on SuH resulting in the translocation of SuH from the cytoplasm to the nucleus. See, *e.g.*, Artavanis-Tsakonas et al., ref. CJ, page 230, right column.

Further, a molecular interaction may be detected using, *e.g.*, *in vitro* binding assays such as those described in the present specification in Sections 6-8, or an immunoassay for detecting SuH in the nucleus, or any other methods well known in the art. A genetic interaction may be detected using *in vivo* assays in which certain phenotypes are detected, *e.g.*, notched wings or wings with a broadening of the veins in the wing. Methods for the detection of molecular and genetic interactions are commonly known to those skilled in the art. As is understood by those in the art, not every genetic interaction will imply a direct molecular interaction, see *e.g.*, Delta-SuH interaction. Moreover, even though not all members of the Notch group may or may not presently be known, the term is nevertheless definite because "acceptability [of a term] depends on 'whether one of ordinary skill in the art would understand what is claimed . . . in light of the specification,' even if experimentation may be needed." Andrew Corp. v. Gabriel Electronics, Inc., 6 U.S.P.Q.2d 2010, 2013 (Fed. Cir. 1988) (citing Seattle Box Co. v. Industrial Crating & Packing, 221 U.S.P.Q. 568, 574 (Fed. Cir. 1984)), cert. denied, 488 U.S. 927 (1988). Accordingly, Applicant respectfully requests withdrawal of this Section 112 rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 90, 92, 98, 103, 106, 109 and 110 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner states:

> The specification is not enabling for the manipulation of cell differentiation by promoting Notch function with any molecule, including "Notch-group" proteins, toporythmic proteins, Delta, or fragments thereof which bind to Notch.
> • • •
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> The specification discloses that Notch and the toporythmic proteins Delta and Serrate interact, at the protein level, when expressed in S2 cells, to bind to each other and to aggregate the cells. There is no further objective evidence, exemplification, or guidance regarding the manipulation of differentiation, the identification of molecules which do so, or the determination of promotion of Notch function and its role in differentiation.
> • • •
> • • •
> • • •
>
> Binding and aggregation could be defined as function, however, there is insufficient guidance regarding the role that measurable binding and aggregation may play in "manipulating differentiation". The specification also provides insufficient guidance regarding the measurement of differentiation. The specification suggests that differentiation may be "assessed visually based on changes in morphology" (page 15), but provides no guidance regarding such changes and what they are indicative of. Further, there is insufficient objective evidence provided to render it predictable that promotion of Notch "function" results in manipulation of differentiation as measured by morphology or any other measure, since it is not clear that aggregation (which is not truly a morphology change) is indicative of differentiation effects. . . Thus, the specification provides guidance with regard to the identification of toporythmic proteins which bind to Notch and effect cell aggregation but, the identification of molecules, toporythmic proteins or fragments which promote Notch function and manipulate differentiation would require undue experimentation due to the unpredictability of the correlation

between binding, aggregation, and Notch function, promotion and differentiation.

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Further, a role in determination of cell fate does not necessarily predict the capability of manipulating differentiation, *per se*. Differentiation is defined as a "process of development in a multicellular organism by which cells become specialized for particular functions. [Differentiation] Requires that there is selective expression of portions of the genome; the fully differentiated state may preceded by a stage in which the cell is already programmed for differentiation but is not yet expressing the characteristic phenotype (determination)." (The Dictionary of Cell Biology, p.61, 1989) Thus, a gene or protein which manipulates or affects determination in not necessarily capable of manipulating or affecting the process of differentiation. Thus, the art would indicate that binding would, indeed, not be expected by one of skill in the art to be predictable of promotion of Notch and predictable of manipulation of differentiation and it would, therefore, require undue experimentation to practice the invention as claimed.

Applicant respectfully disagrees.

Applicant points out that contrary to the Examiner's assertions, it is clear that Notch plays a role in cell differentiation and that the manipulation of cell differentiation can be achieved by manipulating Notch function.

As evidence of the foregoing, the Examiner's attention is invited to the following publications, discussed in detail below:

(1) Lindsell et al., 1995, Cell 80:909-917, ("Lindsell") (reference CQ made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith);

(2) U.S. Patent No. 5,780,300 to Artavanis-Tsakonas et al. ("the '300 patent") (reference CS made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith);

(3) Fortini et al., 1993, Nature 365:555-557, ("Fortini") (reference CW made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith);

(4) Sakano et al., 1997, International Patent Publication WO 97/19172 ("Sakano") (reference CR made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith);

(5) Kopan et al., 1994, Development 120:2385-2396 ("Kopan", reference CO made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith);

(6) Nye et al., 1994, Development 120:2421-2430 ("Nye", reference CP made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith); and

(7) Coffman et al., 1993, Cell 73:659-671 ("Coffman") (reference BM of record).

The Examiner' attention is invited to Lindsell which clearly shows that upon activation of Notch by ligand (in this case Jagged or rat Serrate) binding, differentiation into muscle cells (myogenesis) is prevented. Moreover, on page 915, left column, bottom paragraph, Lindsell states that when the extracellular portion of Notch is deleted, muscle differentiation is perturbed (fragments of Notch lacking the extracellular domain or comprising the intracellular domain are disclosed in the specification, *inter alia*, at page 16, line 22 and at page 5, line 14).

The Examiner's attention is also invited to the'300 patent which also shows that activation of Notch results in manipulation of cell differentiation. In Section 6 of the '300 patent, evidence is presented that demonstrates that expression of a constitutively active form of Notch which lacks the extracellular and transmembrane domains inhibits neural differentiation in the *Drosophila* eye (fragments of Notch lacking the extracellular domain or comprising the intracellular domain are disclosed in the specification, *inter alia*, at page 16, line 22 and at page 5, line 14).

The evidence presented in Fortini also demonstrates that expression of a constitutively active form of Notch which lacks the extracellular and transmembrane domains inhibits neural differentiation in the *Drosophila* eye. Moreover, Fortini on page 556, right column, first full paragraph, proposes that "Notch activation may keep cells in an undetermined state and that activated Notch should cause differentiation delays in *Drosophila*" and that their analysis provides direct evidence to support this proposition (fragments of Notch lacking the extracellular domain or comprising the intracellular domain are disclosed in the specification, *inter alia*, at page 16, line 22 and at page 5, line 14).

The Examiner's attention is also invited to Sakano which discloses experiments in which chimeric human Delta and Serrate proteins were used to manipulate the differentiation state of progenitor cells. The Examiner's attention is invited to Working Examples 10, 11 and 12 on pages 46-53 of the English translation of Sakano submitted with the Japanese language counterpart in the Second Supplemental Information Disclosure Statement. Example 10 shows both chimeric human Delta and Serrate proteins suppressed differentiation of blood progenitor cells by suppressing colony formation. The employed expression vector, HDEXIg, encodes a chimeric Delta protein that is a fusion of full length human Delta and the Fc portion below the hinge portion of human IgG (the engineering of the chimeric protein is described on pages 35-36 of the English translation). The chimeric Serrate protein, encoded by HSEXIg, was a similar fusion (its construction is described on page 39 of the English translation). Example 11 shows that both chimeric Delta and Serrate proteins used above also suppressed differentiation in long term liquid cultures of colony forming undifferentiated blood cells. Example 12 shows that the same chimeric human Delta and Serrate proteins also maintained LTC-IC cells in culture, which cells are believed to be the most undifferentiated blood cell group. Thus, the accumulated data show that Notch signaling plays a fundamental role in the differentiation of uncommitted cells, and that the manipulation of Notch function results in the manipulation of differentiation (proteins that interact with Notch, *e.g.*, proteins that comprise the portions of Delta and Serrate that mediate binding to Notch, are disclosed in the instant specification as agonists of Notch function at page 14, line 18 and page 5, line 13).

The Examiner's attention is also invited to Kopan which shows that a constitutively active form of Notch, Notch IC, represses muscle cell differentiation (myogenesis) in mouse cells and in frog embryos.

The Examiner's attention is further invited to Nye, which shows that NotchIC not only represses myogenesis but neurogenesis as well. Nye also shows that over expression of full-length Notch suppressed neurogenesis (full length Notch protein is disclosed in the specification in Figure 13 and is disclosed as an agonist on page 5, line 13 of the present specification).

The Examiner's attention is further invited to Coffman which shows that a fragment of Notch lacking the extracellular domain suppressed notochord differentiation in midline cells that normally give rise to the notochord; neighboring cells in which the Notch

fragment was not expressed differentiated normally. The differentiation of both ectodermally and mesodermally derived cells appeared to be affected by the expression of the Notch fragment (page 661, column 2). Coffman concludes in the paragraph bridging pages 665-666 that the fragment of Notch lacking the extracellular domain inhibits the differentiation of ectodermal cells and that the Notch fragment is acting to inhibit such cells from committing to certain cell fates.

Applicant respectfully submits that the foregoing demonstrates, consistent with the teaching in the present specification, that the activation of Notch function, *e.g.*, by ligand binding to Notch or expression of an activated form of Notch or otherwise contacting the cell with a toporythmic protein, results in the manipulation of cell differentiation. Moreover, the types of the manipulators of Notch function disclosed in the above-discussed references are disclosed in the present specification. Furthermore, as explained on page 913, right column of Lindsell, Jagged-expressing cells adhered, *i.e.*, aggregated, to Notch-expressing cells, which is consistent with the experimental evidence presented in Sections 6 and 7 of the specification wherein it is shown than Notch-expressing cells and Delta or Serrate-expressing cells also aggregated together. Thus, contrary to the Examiner's assertion, and further in view of the evidence discussed above, such aggregation assays detect physiologically relevant binding.

With regard to the Examiner's statement that it is not clear what is encompassed and included as "Notch function", Applicant respectfully submits that this term is fully enabled by the specification and is known in the art. As discussed above, a Notch function is understood as a function of the Notch protein or an activity of the Notch protein within the Notch signal transduction pathway. Such functions include, but are not limited to, directly binding to Delta, Serrate, Deltex or Suppressor of Hairless, see, *e.g.*, Sections 6-8 of the present specification. Another function includes, but is not limited to, the ability to transduce an extracellular signaling event such that the transcription of certain bHLH genes within the Enhancer of Split complex is activated.

With regard to the Examiner's statement that the specification provides insufficient guidance on measuring differentiation changes, Applicant points out that changes in differentiation can be detected or measured by standard methods well known in the art.[1] It

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[1] Applicant notes that differentiation need not be "measured", as long as changes (continued...)

is commonly known to the skilled artisan, for any particular cell type, how to detect a differentiation change, *e.g.*, changes in expression of differentiation antigens are commonly used, to name but one example. Other examples include changes in any of the commonly known differentiation phenotypes associated with particular cell types. Indeed, the entire classification of cell types is based on their state of differentiation as represented by their differentiation-associated phenotype. As but another example, Sakano in Working Examples 10-12 sets forth well known colony forming assays for detecting the differentiation states of cells obtained from the blood. Applicants respectfully reminds the Examiner that a patent preferably omits what is well known in the art. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

Further, molecules which promote Notch function, and thus, affect differentiation, are disclosed in the specification and/or are known or are readily identified using methods known in the art. The Examiner's attention is invited to the specification at page 11, line 30 to page 12, line 18 wherein it states:

> In another embodiment, Therapeutics which promote Notch function (hereinafter "Agonist Therapeutics") are administered for therapeutic effect; disorders which can thus be treated can be identified by *in vitro* assays such as described in Section 5.1, *infra*. Such Agonist Therapeutics include but are not limited to Notch proteins and derivatives thereof comprising the intracellular domain, Notch nucleic acids encoding the foregoing, and proteins comprising toporythmic protein domains that interact with Notch (*e.g.*, a protein comprising an extracellular domain of a Delta protein or a Delta sequence homologous to *Drosophila* Delta amino acids 1-230 (see Figure 1 and SEQ ID NO:2), or comprising a Serrate sequence homologous to *Drosophila* Serrate amino acids 79-282 (see Figure 5 and SEQ ID NO:4)).

Section 5.1 of the specification states:

> The Agonist Therapeutics of the invention, as described *supra*, promote Notch function. Such Agonist Therapeutics include but are not limited to proteins and derivatives comprising the portions of toporythmic proteins such as Delta or Serrate that mediate binding to Notch, and nucleic acids encoding the foregoing (which can be administered to express their encoded products *in vivo*). In a specific embodiment, such a portion of

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[1](...continued)
therein are detectable.

> Delta is *D. melanogaster* Delta amino acids 1-230 (SEQ ID NO:1) or a portion of a human Delta most homologous thereto. In another specific embodiment, such a portion of Serrate is *D. melanogaster* Serrate amino acids 79-282 (SEQ ID NO:5), or a portion of a human Serrate most homologous thereto. In other specific embodiments, such a portion of Delta or Serrate is the extracellular portion of such protein.
>
> Further descriptions and sources of Therapeutics of the inventions are found in Sections 5.4 through 5.8 herein.

With regard to the Examiner's concerns regarding dosage, Applicant points out that determining appropriate dosages is a matter of routine optimization that can be carried out using standard assays in the art.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. Fields v. Conover, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. Id.

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

Additionally, Applicant points out the following:

(1) evidence leading to the conclusion that human Notch plays a role in determining cell fate (differentiation), specifically, in view of the known role of the *Drosophila* Notch protein in determining cell fate[2], and (i) significant sequence identity indicative of functional conservation between *Drosophila* and human Notch proteins, not only over the entire protein length of approximately 2700 amino acids (see Second Rule 132 Declaration, ¶ 5.5.2; Fourth Rule 132 Declaration, ¶ 8.3), but also between the various functional domains (Second Rule 132 Declaration, ¶ 5.5.3) and in the identical relative arrangement of functional domains throughout the molecules (see Fourth Rule 132 Declaration, ¶¶ 8.1-8.2); (ii) the experimentally proven functional equivalence of the ligand binding domains between human and *Drosophila* Notch proteins (Second Rule 132 Declaration, ¶¶ 5.1-5.1.2 and Exhibit E); (iii) mutations in both human and *Drosophila* Notch proteins result in abnormal cell fate (differentiation) (Second Rule 132 Declaration, ¶ 5.2.1); and (iv) the developmental expression of Notch in vertebrates is similar to that in *Drosophila*, in that both are expressed in developing tissues in which cell-cell interactions are critical (Second Rule 132 Declaration, ¶ 5.3.1); and

(2) evidence demonstrating that increased levels of human Notch in human tissue are associated with the presence of a malignancy (cancer) in such tissue.

With respect to the data demonstrating that measurement of human Notch can be used to detect malignancy, Applicant firstly points out that malignancy is a state commonly known in the art to entail a disturbance in differentiation processes. The data presented in Section 10 of the specification and by way of the Fourth Rule 132 Declaration show that levels of human Notch protein are increased in malignant cells of the human cervix and colon, relative to non-malignant cells from such tissue (Fourth Rule 132 Declaration, ¶¶ 5-5.2). Moreover, Zagouras et al., 1995, Proc. Natl. Acad. Sci. USA 92:6414-6418 (reference CL made of record in the Second Supplemental Information Disclosure Statement submitted concurrently herewith), found that Notch was expressed at a higher level in malignant tissue.

In view of the foregoing, Applicant respectfully submits that the claimed invention is fully enabled and that it would not be undue experimentation to manipulate the

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[2] *See, e.g.*, Artavanis-Tsakonas, 1988, Trends in Genetic 4:95-100 (reference AW of record); specification, p. 1, line 22 through p. 2, line 4; Second Rule 132 Declaration, ¶ 5.2.1.

differentiation state of a cell by contacting the cell with a molecule that promotes Notch function or by contacting the cell with a toporythmic protein.

CONCLUSION

Applicant respectfully requests that the amendments and remarks of the present response be entered and made of record in the file of the above-captioned application. Claims 90, 98, 101, 103-106 and 109-112 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections, allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call Adriane M. Antler at (212) 790-2247 if any questions or issues remain.

Respectfully submitted,

Date December 23, 1998

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S. Leslie Misrock (Reg. No.)

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